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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,070	08/24/2001	Gary Levy		9490

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,070	LEVY, GARY	
	Examin r	Art Unit	
	Shanon Foley	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-10,13 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group III and an antisense oligonucleotide, claims 11-15 in Paper No. 7 is acknowledged. In view of applicant's election of an antisense oligonucleotide, claim 13 is also withdrawn from consideration since the claim is directed to using an antibody. Claims 1-10, 13, and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7. Claims 11, 12, 14, and 15 are under consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the mailing or post office address of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.
>
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a).
>
> It does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and year of its filing.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

It does not include the notary's signature, or the notary's signature is in the wrong place.

It does not include the notary's seal and venue.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is requested to return a copy of the attached Notice to Comply with the response.

In addition, the specification and claims are objected to for failing to adhere to the requirements of the sequence rules, see Figure 2 and sequences in the examples. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. See 37 CFR § 1.821 (a)-(d) and MPEP § 2422.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 12, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is unclear because it cannot be determined how immune coagulation caused by a virus is distinguished from immune coagulation caused by something else, such as endotoxin shock and cancer. This rejection affect dependent claims 12 and 15.

Claim 14 is dependent from claim 1, and lacks antecedent basis for specific limitations. The claim appears to be intended depend from claim 11 and will be treated as such in the interest of compact prosecution. However, because this dependency is only speculative, applicant is required to amend the claim to clarify which limitations are present in the claim.

Claims 14 and 15 are vague and indefinite because it cannot be determined what is being complemented. The claims are drawn to an antisense oligonucleotide that is complementary to the LF-A1 binding element of the promoter region of the fgl-2 gene and an antisense oligonucleotide that is complementary to a LF-A1 gene. The specific oligonucleotide claimed is unclear because DNA sequences usually have two strands, one that complements the other. Therefore, it is unclear which strand the oligonucleotide is complementary to. It is also unclear how many antisense oligonucleotides are being claimed if the claims encompass oligonucleotides that complement either strand. Therefore, the claims could conceivably encompass one oligonucleotide for each strand and each gene, which is at least four oligonucleotides altogether. The individual sequences and the number of oligonucleotides claimed is vague and indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method of preventing or reducing immune coagulation with an inhibitor of LF-A1 gene or protein. The specific inhibitor claimed is an antisense oligonucleotide. As discussed above, it cannot be determined which strand the oligonucleotide is complementing or how many antisense oligonucleotides are being claimed. An embodiment of the invention is found on page 4, lines 9-11, in which the antisense oligonucleotide complements -372 to -306 of the fgl-2 gene sequence. The exact sequence of the oligonucleotide is not defined by the recited region because others skilled in the art may have a different numbering system, so it is unclear where the preferred sequence starts and ends. It is suggested that applicant append the claims to recite a specific SEQ ID NO. to clearly define which sequences and how many are being claimed. Further, the complementary region is not representative of the entire genus claimed. There is no teaching for how one skilled in the art would structurally identify any other antisense oligonucleotide and a definition by function alone "does not suffice, to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lily, 119 F.3 at 1568, 43 USPQ2d at 1406. There is no written description of the full scope of LF-A1 inhibitors and the specification does not convey possession of the entire genus claimed.

Claims 11, 12, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing immune coagulation caused by murine hepatitis

virus strain 3 (MHV-3) with an antisense oligonucleotide complementing the fgl2 prothrombinase gene, does not reasonably provide enablement for preventing or reducing immune coagulation caused by any virus by administering any inhibitor of a LF-A1 gene or protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of preventing or reducing immune coagulation caused by any virus by administering an effective amount of any inhibitor of LF-A1 gene or protein. More specifically, the claims are drawn to administering an antisense oligonucleotide that is complementary to the LF-A1 binding element of the fgl-2 gene or an oligonucleotide that is complementary to a nucleic acid sequence from the LA-F1 gene. The nature of the invention is drawn to preventing or reducing immune coagulation in caused by human hepatitis with an antisense oligonucleotide that complements various regions within fgl-2. There are no working examples or teaching in the specification that discusses inhibition of immune coagulation caused by other viruses or pathogens.

The skilled artisan would be unable to make the instantly claimed antisense oligonucleotide because it is unclear which strand the antisense oligonucleotide is complementary and the exact location of the complementation. In addition, it is noted that the sequences encoding the fgl-2 genes are dissimilar, see Ding et al. (abstract no: 365, reference no: XP-000929678 of the IDS). Ding et al. teaches that the sequence similarity between fgl-2 and hfgl-2 proteins is over 70% and that these proteins are 90% identical in amino acid sequence, but only at the C-terminal end. Therefore, the exact sequence of the antisense oligonucleotide

claimed, which is vague and indefinite, would not correlate to the human sequence of fgl-2 because of the 30% difference between the residues between the mouse and human fgl-2.

The specification teaches that the nucleocapsid protein of MHV-3 induces transcription of fgl-2. This is also taught in the art, see Ning et al. (Journal of Biological Chemistry. 1999; 274 (15): 9930-9936). However, the skilled artisan would doubt that the instant antisense oligonucleotide would be effective against immune anticoagulation in every type of human hepatitis. The working examples in the specification teach that the induction of fgl-2 is not always present in murine models of hepatitis virus, see pages 24-27, which discusses the inability of MHV-2 to induce transcription of fgl-2. In addition, it is not clear in the art whether or not the core antigen of HBV induces transcription of hfgl-2, see the paragraph bridging pages 9934-9935 of Ning et al., so it cannot be predicted whether this gene is also the cause for greater pathology in every type of human hepatitis. The working examples and the art demonstrate a lack of predictability for fgl-2 expression and its putative role in every strain of mouse hepatitis. Therefore, the skilled artisan would not conclude that the instant antisense oligonucleotide would be effective in human hepatitis because of the discrepancies between human and murine sequences and the different functions of fgl-2 in murine hepatitis.

Further, there are no working examples demonstrating inhibition or prevention of immune coagulation with the instant oligonucleotide in humans. There is no teaching in the specification or working examples demonstrating that the induction of fgl-2 induces immune coagulation in as a result of human hepatitis infection. There is also no indication that administering the instant antisense oligonucleotide to humans suffering from hepatitis infection would not adversely affect normal immune functioning. The specification teaches that the

immune coagulation system is crucial for normal immune functioning against bacterial and viral pathogens, see pages 1-4. There is no indication that administering the instant oligonucleotide would not cause detrimental effects on normal immune system functioning.

Therefore, due to the scope of the claims encompassing preventing and reducing all forms of immune coagulation caused by any virus by administering an antisense oligonucleotide, the lack of definitive sequences for the antisense oligonucleotide, the lack of data for reducing or inhibiting immune coagulation caused by human hepatitis, the lack of prior art teaching that the LF-A1 or fgl-2 gene induces immune coagulation in hepatitis infection, and the lack of predictability for what kind of effect the antisense oligonucleotide inhibitor would have on normal immune functioning, it is determined that an undue amount of experimentation would be required of the skilled artisan to make and practice the invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11, 12, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ding et al. (Journal of Virology. 1997; 71 (12): 9223-9230) and Mizutani et al. (Journal of Veterinary Medical Science. 1994; 56 (2): 211-215, abstract only).

The claims are drawn to a method of reducing immune coagulation caused by a hepatitis virus by administering an antisense oligonucleotide that is complementary to the LF-A1 binding element of the promoter region of the fgl-2 gene.

Ding et al. teaches immune coagulation caused by murine hepatitis virus strain 3 (MHV-3) is caused by induction of fgl-2 prothrombinase gene. Ding et al. does not teach reducing immune coagulation with an antisense oligonucleotide that complements the promoter of the fgl-2 gene.

However, Mizutani et al. teaches an antisense oligonucleotide that is directed against the nucleocapsid protein of MHV reduces viral transcription and replication.

One of ordinary skill in the art at the time the invention was made would have been motivated to reduce immune coagulation caused by MHV to prevent fulminant liver failure. The skilled artisan would have been further motivated to use an antisense oligonucleotide to reduce immune coagulation induced by fgl-2 because these substances are known to inhibit the genes they bind to and they are easily synthesized. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Ding et al. teaches that the induction of fgl-2 RNA transcripts promotes immune coagulation and Mizutani et al. teaches inhibition of viral transcription with an antisense oligonucleotide. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
June 26, 2002

JAMES HOUSEL 7/1/02
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600